REMARKS

Correction of Inventorship under 37 CFR §1.48(b)

Applicants request that several inventors be deleted, as these inventors' inventions are no longer being claimed in the present application as a result of prosecution. The fee as set forth in 37 CFR § 1.17(i) is submitted herewith.

Priority

The Examiner asserts that the priority date of the application is August 24, 2000. In addition, the Examiner asserts that the results of the assay of Example 18 are lacking utility and are not enabling.

As discussed in the Preliminary Amendment submitted September 3, 2002, the instant application is a continuation of, and claims priority under 35 U.S.C. § 120 to, US Application 10/006867 filed 12/6/2001, which is a continuation of, and claims priority under 35 U.S.C. § 120 to, PCT Application PCT/US00/23328 filed 8/24/2000, which is a continuation-in-part of, and claims priority under 35 U.S.C. § 120 to U.S. Application 09/380137 filed 8/25/99, which is the National Stage filed under 35 U.S.C. §371 of PCT Application PCT/US99/12252 filed 6/2/1999, which claims priority under 35 U.S.C. §119 to U.S. Provisional Application 60/090688 filed 6/25/1998.

Applicants submit that for the reasons stated below, the claimed polypeptides have a credible, substantial, and specific utility. The sequence of SEQ ID NO: 48 was first disclosed in US Provisional Application 60/090688 filed 6/25/1998. The data in Example 18 (Tumor Versus Normal Differential Tissue Expression Distribution), relied on in part for the utility of the claimed polypeptides, were first disclosed in PCT Application PCT/US00/23328 filed 8/24/2000, on page 93, line 3, through page 96, line 35.

Information Disclosure Statement

The Examiner states that the Information Disclosure Statement filed September 17, 2002 has been considered. However, the Examiner asserts that the BLAST results provided with the Information Disclosure Statement do not give sufficient identifying information such that the Examiner cannot determine if the sequences constitute prior art. The Examiner also notes that

U.S. Patent No. 5,546,637 was cited in the Information Disclosure Statement as being issued to Jacobs et al. on July 16, 1997 but was in fact issued to Niedecker on August 20, 1996.

Applicants submit herewith a new Information Disclosure Statement providing the accession numbers, sequences, and publication dates of the sequences identified in the BLAST search. Applicants have also corrected a typographical error in the Information Disclosure Statement in which the Jacobs patent was listed as U.S. Patent No. 5,546,637 rather than U.S. Patent No. 5,536,637.

Objections to the Specification

The Examiner asserts that the title of the application is not descriptive. Applicants have amended the title to address the Examiner's concerns.

The Examiner also notes that the specification includes browser-executable hyperlinks. Applicants have amended the specification to address the Examiner's concern. In particular, Applicants have replaced the hyperlink with text that describes the location of the website. The amended text no longer constitutes browser executable code.

Utility

Claims 1 - 13 were rejected under 35 U.S.C. 101 on the assertion that the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

The Examiner maintains that the asserted utility in diagnosis and treatment is not substantial. First, the Examiner asserts that it is unclear whether the changes in expression of the PRO994-encoding cDNA are statistically significant, and whether such changes in the expression of the cDNA are correlated with changes in expression of the encoded protein. The Examiner asserts that the changes in PRO994 expression, even if they are statistically significant, are at the level of nucleic acid, which is not necessarily correlated with protein expression or activity. Second, the Examiner asserts that cDNA libraries have an inherent bias to them, therefore the results obtained in a cDNA library-based differential expression assay may not be representative of actual changes in the tissues from which the libraries are created. Ohara et al. (2001, Nucleic Acids Research 29(4):e22 p. 1 - 8, see especially Introduction) is cited as teaching that cDNA libraries under-represent larger cDNAs and those that contain internal restriction sites. Further, the Examiner asserts that the specification does not disclose the biological significance of the

changes in expression. In particular, the Examiner asserts that the specification does not disclose whether the increase in PRO994 expression in rectal tumor, or the decrease of PRO994 expression in stomach tumor, is a cause of the tumors or a consequence of them. According to the Examiner, since PRO994 expression increases in one tumor and decreases in another, its expression level cannot be considered as a marker for the presence or absence of a tumor.

Utility – Legal Standard

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic tool without also identifying the condition that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. § 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, *any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient,* at least with regard to defining a 'substantial' utility." (M.P.E.P. § 2107.01, emphasis added).

The mere consideration that further experimentation might be performed to more fully develop the claimed subject matter does not support a finding of lack of utility. M.P.E.P. § 2107.01 III cites *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995) in stating that "Usefulness in patent law ... necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans." Further, "[T]o violate § 101 the claimed device must be totally incapable of achieving a useful result" *Juicy Whip Inc. v. Orange Bang Inc.*, 51 USPQ2d

1700 (Fed. Cir. 1999), *citing Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed.Cir.1992).

Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. § 2107 II(B)(1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose ... and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Finally, in assessing the credibility of the asserted utility, the M.P.E.P. states that "to overcome the presumption of truth that an assertion of utility by the applicant enjoys" the PTO must establish that it is "more likely than not that one of ordinary skill in the art would doubt (i.e., "question") the truth of the statement of utility." M.P.E.P. § 2107.02 III A. The M.P.E.P. cautions that:

> Rejections under 35 U.S.C. 101 have been **rarely sustained** by federal courts. Generally speaking, **in these rare cases**, the 35 U.S.C. 101 rejection was sustained either because the **applicant ... asserted a utility that could only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art**. M.P.E.P. § 2107.02 III B. (underline emphasis in original, bold emphasis added); citing *In re Gazave*, 379 F.2d 973, 978, 154 USPQ 92, 96 (CCPA 1967).

Utility need NOT be Proved to a Statistical Certainty – a Reasonable Correlation between the Evidence and the Asserted Utility is Sufficient

An Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). *See, also In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977). Compliance with 35 U.S.C. § 101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or "more likely than

not" standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty**. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. M.P.E.P. at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

The PTO has the initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Applicant to provide rebuttal evidence. *Id.* As stated in the M.P.E.P., such rebuttal evidence does not need to absolutely prove that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility.

In *Fujikawa v. Wattanasin*, 93 F.3d 1559, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996), the Court of Appeals for the Federal Circuit upheld a PTO decision that *in vitro* testing of a novel pharmaceutical compound was sufficient to establish practical utility, stating the following rule:

> [T]esting is often required to establish practical utility. But the test results **need not absolutely prove** that the compound is pharmacologically active. All that is required is that the tests be "*reasonably* indicative of the desired [pharmacological] response." In other words, there must be **a sufficient correlation** between the tests and an asserted pharmacological activity so as to convince those skilled in the art, **to a reasonable probability**, that the novel compound will exhibit the asserted pharmacological behavior." *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1564, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996) (internal citations omitted, bold emphasis added, italics in original).

While the *Fujikawa* case was in the context of utility for pharmaceutical compounds, the principals stated by the Court are applicable in the instant case where the asserted utility is for a therapeutic and diagnostic use – utility does not have to be established to an absolute certainty, rather, the evidence must convince a person of skill in the art "to a reasonable probability." In addition, the evidence need not be direct, so long as there is a "sufficient correlation" between the tests performed and the asserted utility.

The Court in *Fujikawa* relied in part on its decision in *Cross v. Iizuka*, 753 F.2d 1040, 224 U.S.P.Q. 739 (Fed. Cir. 1985). In *Cross*, the Appellant argued that basic *in vitro* tests conducted in cellular fractions did not establish a practical utility for the claimed compounds. Appellant argued that more sophisticated *in vitro* tests using intact cells, or *in vivo* tests, were necessary to establish a practical utility. The Court in *Cross* rejected this argument, instead favoring the argument of the Appellee:

> *[I]n vitro* results...are generally predictive of *in vivo* test results, i.e., there is a **reasonable correlation** therebetween. Were this not so, the testing procedures of the pharmaceutical industry would not be as they are. [Appellee] has not urged, and rightly so, that there is an invariable exact correlation between *in vitro* test results and *in vivo* test results. Rather, [Appellee's] position is that successful *in vitro* testing for a particular pharmacological activity establishes a **significant probability** that *in vivo* testing for this particular pharmacological activity will be successful. *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 U.S.P.Q. 739 (Fed. Cir. 1985) (emphasis added).

The *Cross* case is very similar to the present case. Like *in vitro* testing in the pharmaceutical industry, those of skill in the field of biotechnology rely on the reasonable correlation that exists between gene expression and protein expression (see below). Were there no reasonable correlation between the two, the techniques that measure gene levels such as microarray analysis, differential display, and quantitative PCR would not be so widely used by those in the art. As in *Cross*, Applicants here do not argue that there is "an invariable exact correlation" between gene expression and protein expression. Instead, Applicants' position detailed below is that a measured change in gene expression in cancer cells establishes a "significant probability" that the expression of the encoded polypeptide in cancer will also be changed based on "a reasonable correlation therebetween."

Taken together, the legal standard for demonstrating utility is a relatively low hurdle. An Applicant need only provide evidence such that it is **more likely than not that a person of skill in the art would be convinced, to a reasonable probability, that the asserted utility is true**. The evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. The Applicant **does not need to provide evidence such that it establishes an asserted utility as a matter of statistical certainty.**

Even assuming that the PTO has met its initial burden to offer evidence that one of ordinary skill in the art would reasonably doubt the truth of the asserted utility, Applicants assert that they have met their burden of providing rebuttal evidence such that it is more likely than not those skilled in the art, to a reasonable probability, would believe that the claimed invention is useful as a diagnostic tool for cancer.

Substantial Utility

Summary of Applicants' Arguments and the PTO's Response

In an attempt to clarify Applicants' argument, Applicants offer a summary of their argument and the disputed issues involved. Applicants assert they have provided reliable evidence that mRNA for the PRO994 polypeptide is more highly expressed in normal stomach tissue or rectum tumor compared to stomach tumor or normal rectum tissue respectively, and therefore the claimed polypeptides are useful as diagnostic tools and therapeutic agents. Applicants are not asserting that the claimed polypeptides will necessarily provide a definitive diagnosis of cancer, but rather that they are useful, alone or in combination with other diagnostic tools to assist in the diagnosis of certain cancers. Applicants' asserted utility rests on the following argument:

1. Applicants have provided reliable evidence that mRNA for the PRO994 polypeptide is more highly expressed in normal stomach tissue or rectum tumor compared to stomach tumor or normal rectum tissue respectively;

2. Applicants assert that it is well-established in the art that a change in the level of mRNA encoding a particular protein, e.g. an increase or a decrease generally leads to a corresponding change in the level of the encoded protein, e.g. an increase or a decrease;

3. Applicants submit that the claimed polypeptides have utility regardless of whether or not their differential expression is the cause of stomach tumors or rectal tumors.

Applicants understand the PTO to be making several arguments regarding the utility of the claimed polypeptides:

1. The PTO has challenged the evidence reported in Example 18 on the assertion that the data is not statistically significant.

2. The PTO asserts that Applicants have not provided evidence showing that the PRO994 polypeptide is more highly expressed in normal stomach tissue or rectum tumor compared to stomach tumor or normal rectum tissue respectively.

3. The PTO asserts that cDNA libraries have an inherent bias to them and the results obtained in a cDNA library-based differential expression assay may not be representative of actual changes in the tissues from which the libraries are created.

4. The PTO asserts that the specification does not disclose whether the differential expression of the claimed polypeptides is a cause of tumors or a consequence of them.

As detailed below, Applicants submit that the PTO has failed to meet its initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Applicants maintain that the data in Example 18 provides reliable evidence that the mRNA encoding the PRO994 protein is more highly expressed in normal stomach tissue or rectum tumor compared to stomach tumor or normal rectum tissue respectively. In particular, in contrast to the Examiner's assertions that cDNA libraries are inherently biased, Applicants maintain that quantitative PCR amplification reactions with cDNA libraries are an accurate way to determine the mRNA expression levels. Applicants submit that given the well-established correlation between a change in the level of mRNA with a corresponding change in the levels of the encoded protein, the PRO994 protein is likely differentially expressed in certain tumors. Applicants also maintain that the claimed polypeptides have utility regardless of whether or not their differential expression is the cause of stomach tumors or rectal tumors. Finally, even if the PTO has met its initial burden, Applicants have submitted enough rebuttal evidence to establish that it is **more likely than not** that a person of skill in the art would be convinced, **to a reasonable probability,** that the asserted utility is true. As stated above, **the standard for establishing an asserted utility is not statistical or absolute certainty.**

Applicants have established that the Gene Encoding the PRO994 Polypeptide is Differentially Expressed in Certain Cancers compared to Normal Tissue

Applicants first address the PTO's argument that the evidence of differential expression of the gene encoding the PRO994 in normal stomach tissue or rectum tumor compared to stomach tumor or normal rectum tissue respectively is insufficient.

Applicants maintain that the data in Example 18 are sufficient to establish that the mRNA encoding the PRO994 polypeptide is more highly expressed in normal stomach tissue or rectum tumor compared to stomach tumor or normal rectum tissue respectively. Gene expression was analyzed using standard semi-quantitative PCR amplification reactions of cDNA libraries isolated from different human tumor and normal human tissue samples. Identification of the differential expression of the PRO994 polypeptide-encoding gene in tumor tissue compared to the corresponding normal tissue renders the claimed polypeptides useful as a diagnostic tool for the determination of the presence or absence of tumor. In support, submit as Exhibit 1 a first Declaration of J. Christopher Grimaldi, an expert in the field of cancer biology. This declaration explains the importance of the data in Example 18, and how differential gene and protein expression studies are used to differentiate between normal and tumor tissue (see Declaration, paragraph 7).

In paragraph 5 of his declaration, Mr. Grimaldi states that the gene expression studies reported in Example 18 of the instant application were made from pooled samples of normal and of tumor tissues. Mr. Grimaldi explains that:

> The DNA libraries used in the gene expression studies were made from pooled samples of normal and of tumor tissues. *Data from pooled samples is more likely to be accurate than data obtained from a sample from a single individual.* That is, the detection of variations in gene expression is likely to represent a more generally relevant condition when pooled samples from normal tissues are compared with pooled samples from tumors in the same tissue type. (Paragraph 5) (emphasis added).

The use of pooled samples increases the accuracy of the experiment. In paragraphs 6 and 7, Mr. Grimaldi explains that the semi-quantitative analysis employed to generate the data of Example 18 is sufficient to determine if a gene is over- or under-expressed in tumor cells compared to corresponding normal tissue. He states that any visually detectable difference seen between two samples is indicative of at least a two-fold difference in cDNA between the tumor tissue and the counterpart normal tissue. Thus, the results of Example 18 reflect at least a two-fold difference between normal and tumor samples.

In addition, Applicants note that Dr. Grimaldi also states that the results of the gene expression studies indicate that the genes of interest "can be used to differentiate tumor from

normal," thus establishing their reliability. He explains that "The precise levels of gene expression are irrelevant; what matters is that there is a relative difference in expression between normal tissue and tumor tissue." (Paragraph 7). Thus, since it is the relative level of expression between normal tissue and suspected cancerous tissue that is important, the precise level of expression in normal tissue is irrelevant. Likewise, there is no need for quantitative data to compare the level of expression in normal and tumor tissue. As Mr. Grimaldi states, "If a difference is detected, this indicates that the gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes, to screen samples to differentiate between normal and tumor."

Applicants submit that the declaration of Mr. Grimaldi is based on personal knowledge of the relevant facts at issue. Mr. Grimaldi is an expert in the field and conducted or supervised the experiments at issue. Applicants remind the PTO that "[o]ffice personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned." PTO Utility Examination Guidelines (2001) (emphasis added). In addition, declarations relating to issues of fact should not be summarily dismissed as "opinions" without an adequate explanation of how the declaration fails to rebut the Examiner's position. *In re Alton* 76 F.3d 1168 (Fed. Cir. 1996). Furthermore, Applicants note that the position of Mr. Grimaldi is supported by the Alberts textbook, the Zhigang reference, the Meric textbook, and the Lewin textbook discussed herein.

The Examiner asserts that cDNA libraries have an inherent bias to them and that, therefore, the results obtained in a cDNA library-based differential expression assay may not be representative of actual changes in the tissues from which the libraries are created. Ohara et al. is cited as (2001, Nucleic Acids Research 29(4):e22 p. 1 - 8, see especially Introduction) teaching that cDNA libraries under-represent larger cDNAs and those that contain internal restriction sites.

Applicants note that as provided in Paragraph [0530] of the specification, the PCR products evaluated in the quantitative PCR reactions described in Example 18 were 200 to 600 nucleotides in length. Such short amplification products would not be subject to the under-representation of long cDNAs referred to by the Examiner. Furthermore, with respect to the under-representation relating to internal restriction cites referred to by the Examiner, such under-

representation is only an issue when the cDNAs are being cloned into a vector. In the quantitative PCR reactions of Example 18, the amplification products were not cloned into a vector. Instead, the amplification reaction products were run directly on an agarose gel. Furthermore, the under-representation which the Examiner is referring to is the under-representation of long cDNAs relative to other distinct cDNAs which are shorter. Such under-representation would not affect the relative levels of the same cDNA (i.e. the cDNA made from mRNA encoding the PRO994 protein) in one tissue type versus another tissue type since the cDNA is the same length in both samples. Thus, the comparison of the level of cDNA made from mRNA encoding the PRO994 protein in normal tissue samples relative to the level of the same cDNA in tumor samples would not be impacted by the bias alleged by the Examiner.

In conclusion, Applicants submit that the evidence reported in Example 18, combined with the first Grimaldi Declaration, establishes that there is at least a two-fold difference in PRO994 cDNA between normal stomach tissue or rectum tumor compared to stomach tumor or normal rectum tissue respectively. Furthermore, the data in Example 18 reliably indicates that the PRO994 mRNA is differentially expressed. Therefore, it follows that expression levels of the PRO994 polypeptide can be used to distinguish normal stomach tissue or rectum tumor from stomach tumor or normal rectum tissue respectively. The PTO has not offered any significant arguments or evidence to the contrary.

Applicants have established that the Accepted Understanding in the Art is that there is a Direct Correlation between mRNA Levels and the Level of Expression of the Encoded Protein

Applicants submit that it is well-established in the art that a change in the level of mRNA for a particular protein, generally leads to a corresponding change in the level of the encoded protein. Given Applicants' evidence of differential expression of the mRNA for the PRO994 polypeptide in stomach tumor and rectum tumor, it is more likely than not that the PRO994 polypeptide is also differentially expressed.

Applicants submit herewith a copy of a second Declaration by J. Christopher Grimaldi, an expert in the field of cancer biology (attached as Exhibit 2). As stated in paragraph 5 of the declaration, "Those who work in this field are well aware that in the vast majority of cases, when a gene is over-expressed...the gene product or polypeptide will also be over-expressed.... This same principal applies to gene under-expression." Further, "the detection of increased mRNA

expression is expected to result in increased polypeptide expression, and the detection of decreased mRNA expression is expected to result in decreased polypeptide expression. The detection of increased or decreased polypeptide expression can be used for cancer diagnosis and treatment." The references cited in the declaration and submitted herewith support this statement. Applicants maintain that antibodies against the encoded polypeptides can be used for diagnostic and therapeutic purposes.

As discussed above, Applicants submit that the declaration of Mr. Grimaldi is based on personal knowledge of the relevant facts at issue. Mr. Grimaldi is an expert in the field and conducted or supervised the experiments at issue. Applicants remind the PTO that "[o]ffice personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned." PTO Utility Examination Guidelines (2001) (emphasis added). The PTO has not supplied any reasons or evidence to question the accuracy of the facts upon which Mr. Grimaldi based his statements. Mr. Grimaldi has personal knowledge of the relevant facts, has based his opinion on those facts, and, as discussed herein, the PTO has not offered sufficient evidence to reject either the underlying facts or his opinion. Therefore, the PTO should accept Mr. Grimaldi's statement that "in the vast majority of cases, when a gene is over-expressed...the gene product or polypeptide will also be over-expressed.... This same principal applies to gene under-expression."

Applicants also submit herewith a copy of the declaration of Paul Polakis, Ph.D. (attached as Exhibit 3), an expert in the field of cancer biology. As stated in paragraph 6 of his declaration:

> Based on my own experience accumulated in more than 20 years of research, including the data discussed in paragraphs 4 and 5 above [showing a positive correlation between mRNA levels and encoded protein levels in the vast majority of cases] and my knowledge of the relevant scientific literature, it is my considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell. In fact, *it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein.* (Emphasis added).

Dr. Polakis acknowledges that there are published cases where such a correlation does not exist, but states that it is his opinion, based on over 20 years of scientific research, that "such

reports are exceptions to the commonly understood general rule that increased mRNA levels are predictive of corresponding increased levels of the encoded protein." (Polakis Declaration, paragraph 6).

As discussed above, Applicants submit that the declaration of Dr. Polakis is based on personal knowledge of the relevant facts at issue. Dr. Polakis is an expert in the field. Applicants remind the PTO that "[o]ffice personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned." PTO Utility Examination Guidelines (2001) (emphasis added). The PTO has not supplied any reasons or evidence to question the accuracy of the facts upon which Dr. Polakis based his opinion. Dr. Polakis has personal knowledge of the relevant facts, has based his opinion on those facts, and, as discussed herein, the PTO has not offered sufficient evidence to reject either the underlying facts or his opinion. Therefore, the PTO should accept Dr. Polakis' statement that "it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein."

Thus, contrary to the position of the PTO, the correlation between mRNA levels and protein levels is supported by the art. The statements of Grimaldi and Polakis are supported by the teachings in Molecular Biology of the Cell, a leading textbook in the field (Bruce Alberts, *et al.*, Molecular Biology of the Cell (3rd ed. 1994) (submitted herewith as Exhibit 4) and (4th ed. 2002) (submitted herewith as Exhibit 5)). Figure 9-2 of Exhibit 4 shows the steps at which eukaryotic gene expression can be controlled. The first step depicted is transcriptional control. Exhibit 4 provides that "[f]or most genes transcriptional controls are paramount. This makes sense because, of all the possible control points illustrated in Figure 9-2, only transcriptional control ensures that no superfluous intermediates are synthesized." Exhibit 4 at 403 (emphasis added). In addition, the text states that "Although controls on the initiation of gene transcription are the predominant form of regulation for most genes, other controls can act later in the pathway from RNA to protein to modulate the amount of gene product that is made." Exhibit 4 at 453 (emphasis added). Thus, as established in Exhibit 4, the predominant mechanism for regulating the amount of protein produced is by regulating transcription initiation.

In Exhibit 5, Figure 6-3 on page 302 illustrates the basic principle that there is a correlation between increased gene expression and increased protein expression. The

accompanying text states that "a cell can change (or regulate) the expression of each of its genes according to the needs of the moment – *most obviously by controlling the production of its mRNA*." Exhibit 5 at 302 (emphasis added). Similarly, Figure 6-90 on page 364 of Exhibit 5 illustrates the path from gene to protein. The accompanying text states that while potentially each step can be regulated by the cell, "the initiation of transcription is the most common point for a cell to regulate the expression of each of its genes." Exhibit 5 at 364 (emphasis added). This point is repeated on page 379, where the authors state that of all the possible points for regulating protein expression, "[f]or most genes transcriptional controls are paramount." Exhibit 5 at 379 (emphasis added).

Further support for Applicants' position can be found in the textbook, Genes VI, (Benjamin Lewin, Genes VI (1997)) (submitted herewith as Exhibit 6) which states "having acknowledged that control of gene expression can occur at multiple stages, and that production of RNA cannot inevitably be equated with production of protein, it is clear that the overwhelming majority of regulatory events occur at the initiation of transcription." *Genes VI* at 847-848 (emphasis added).

Additional support is also found in Zhigang *et al.*, World Journal of Surgical Oncology 2:13, 2004, submitted herewith as Exhibit 7. Zhigang studied the expression of prostate stem cell antigen (PSCA) protein and mRNA to validate it as a potential molecular target for diagnosis and treatment of human prostate cancer. The data showed "a high degree of correlation between PSCA protein and mRNA expression" Exhibit 7 at 4. Of the samples tested, 81 out of 87 showed a high degree of correlation between mRNA expression and protein expression. The authors conclude that "it is demonstrated that PSCA protein and mRNA overexpressed in human prostate cancer, and that the increased protein level of PSCA was resulted from the upregulated transcription of its mRNA." Exhibit 7 at 6. Even though the correlation between mRNA expression and protein expression occurred in 93% of the samples tested, not 100%, the authors state that "PSCA may be a promising molecular marker for the clinical prognosis of human Pca and a valuable target for diagnosis and therapy of this tumor." Exhibit 7 at 7.

Further, Meric *et al.*, Molecular Cancer Therapeutics, vol. 1, 971-979 (2002), submitted herewith as Exhibit 8, states the following:

> The **fundamental principle** of molecular therapeutics in cancer is to exploit the differences in gene expression between cancer cells and normal cells...[M]ost efforts have concentrated on identifying differences in gene expression at the level of mRNA, which can be attributable to either DNA amplification or to differences in transcription. Meric *et al.* at 971 (emphasis added).

Those of skill in the art would not be focusing on differences in gene expression between cancer cells and normal cells if there were no correlation between gene expression and protein expression.

Together, the declarations of Grimaldi and Polakis, the accompanying references, and the excerpts and references provided above all establish that the accepted understanding in the art is that there is a reasonable correlation between changes in gene expression and the level of the encoded protein.

In addition to the foregoing, Dr. Ashkenazi's Declaration, submitted herewith as Exhibit 9, points out that there are situations where it is useful to quantitate both nucleic acid levels and protein levels. In particular, Dr. Ashkenazi points out that in situations where over-expression of the gene product does not parallel gene amplification in certain tumor types but does so in others, then parallel monitoring of gene amplification and gene product over-expression enables more accurate tumor classification and hence better determination of suitable therapy. In such situations, absence of over-expression is crucial information for the practicing clinician. If a gene is amplified but the corresponding gene product is not over-expressed, the clinician accordingly will decide not to treat a patient with agents that target that gene product. Thus, the claimed polypeptides have utility even if polypeptide expression does not correlate with mRNA levels. Applicants maintain, however, that in most instances differential expression of a nucleic acid results in differential expression of the encoded polypeptide.

The Examiner asserts that the specification does not disclose the biological significance of the changes in expression. In particular, the Examiner asserts that the specification does not disclose whether the increase in PRO994 expression in rectal tumor, or the decrease of PRO994 expression in stomach tumor, is a cause of the tumors or a consequence of them.

As an initial matter, Applicants submit that whether or not PRO994 is the causative agent for stomach tumor or rectum tumor does not impact its use as a diagnostic tool for cancer. One does not need to know what the consequence of the differential expression is, in order to exploit

the differential expression to distinguish tumor from normal tissue. In fact the Revised Interim Utility Guidelines promulgated by the PTO recognize that proteins which are differentially expressed in cancer have utility. (*See* the caveat in Example 12 which state that the utility requirement is satisfied where a protein is expressed in melanoma cells but not on normal skin and antibodies against the protein can be used to diagnose cancer.) In addition, while Applicants appreciate that actions taken in other applications are not binding on the PTO with respect to the present application, Applicants note that the PTO has issued several patents claiming differentially expressed polypeptides. (*See, e.g.,* U.S. Patent No. 6,414,117 and U.S. Patent No. 6,124,433, attached hereto as Exhibits 10 and 11.)

The Examiner also asserts that because PRO994 expression increases in one tumor and decreases in another, its expression level cannot be considered as a marker for the presence or absence of a tumor. Applicants maintain that one using the claimed polypeptides as a diagnostic tool would know whether the sample being assessed originates from stomach or from rectum. Accordingly, one can readily assess whether the level of the claimed polypeptides are under-expressed in a sample originating from stomach (indicating the individual from whom the sample was taken may have stomach cancer) or whether the claimed polypeptides are over-expressed in a sample originating from rectum (indicating that the individual from whom the sample was taken may have a rectal tumor). In view of the foregoing, Applicants maintain that the claimed polypeptides can be used as a marker for the presence or absence of stomach tumor or rectum tumor.

The Arguments made by the PTO are Not Sufficient to satisfy the PTO's Initial Burden of Offering Evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility"

As stated above, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or "more likely than not" standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty**. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. M.P.E.P. at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

The PTO has the initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Applicant to provide rebuttal evidence. *Id.* As stated in the M.P.E.P., such rebuttal evidence does not need to absolutely prove that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility.

The PTO has not offered any arguments or cited any references to establish "that one of ordinary skill in the art would reasonably doubt" that a polypeptide differentially expressed in certain tumors can be used as a diagnostic or therapeutic tool. Given the lack of support for the PTO's position, Applicants submit that the PTO has not met its initial burden of overcoming the presumption that the asserted utility is sufficient to satisfy the utility requirement. And even if the PTO has met that burden, the Applicants' supporting rebuttal evidence is sufficient to establish that one of skill in the art would be more likely than not to believe that the claimed polypeptides can be used as diagnostic or therapeutic tools for cancer, particularly stomach tumor or rectum tumor.

Specific Utility

The Asserted Substantial Utilities are Specific to the Claimed Polypeptides

Applicants have provided a specific utility for the polypeptides. Specific Utility is defined as utility which is "specific to the subject matter claimed," in contrast to "a general utility that would be applicable to the broad class of the invention." M.P.E.P. § 2107.01 I. Applicants submit that the evidence of differential expression of the PRO994 gene in certain types of tumor cells, along with the declarations and references discussed above, provide a specific utility for the claimed polypeptides.

As discussed above, there are significant data which show that the PRO994 gene is more highly expressed in normal stomach tissue or rectum tumor compared to stomach tumor or normal rectum tissue respectively. These data are strong evidence that the PRO994 gene is associated with stomach tumors or rectum tumors. Thus, Applicants submit that they have provided evidence associating the PRO994 gene with a specific disease. The asserted utility as a diagnostic tool for cancer, particularly stomach tumor or rectum tumor, is a specific utility – it is not a general utility that would apply to the broad class of polypeptides.

Conclusion

The PTO has asserted several arguments to support its conclusion that the differential expression of PRO994 is not sufficient to establish utility for the claimed polypeptides:

1. The PTO has challenged the evidence reported in Example 18 on the assertion that the data is not statistically significant.

2. The PTO asserts that Applicants have not provided evidence showing that the PRO994 polypeptide is more highly expressed in normal stomach tissue or rectum tumor compared to stomach tumor or normal rectum tissue respectively.

3. The PTO asserts that cDNA libraries have an inherent bias to them and the results obtained in a cDNA library-based differential expression assay may not be representative of actual changes in the tissues from which the libraries are created.

4. The PTO asserts that the specification does not disclose whether the differential expression of the claimed polypeptides is a cause of tumors or a consequence of them.

Applicants have addressed each of these arguments in turn. First, the Applicants provided a first Declaration of Chris Grimaldi stating that the data in Example 18 are real and significant. This declaration also indicates that given the relative difference in expression levels, the disclosed polypeptides have utility as cancer diagnostic tools. The PTO has not offered any substantial reason or evidence to question the data in Example 18, or the first Grimaldi Declaration.

Second, Applicants have shown that the second Grimaldi Declaration and Polakis Declaration, the accompanying references, as well as the excerpts and references cited above, demonstrate that it is well-established in the art that a change in mRNA levels generally correlates to a corresponding change in the encoded protein levels. The PTO has not offered any

substantial reason or evidence to question these declarations and supporting references. One of skill in the art will recognize that polypeptides differentially expressed in certain cancers have utility as diagnostic or therapeutic tools for cancer.

Applicants have established that the data in Example 18 accurately reflect differential mRNA levels and are not influenced by the bias which the Examiner asserts is present in cDNA libraries.

Applicants have also established that the claimed polypeptides are useful regardless of whether or not they are the causative agent of cancer.

Applicants have pointed out that the substantial utilities described above are specific to the claimed polypeptides because the PRO994 gene is differentially expressed in stomach tumors or rectum tumors compared to the corresponding normal cells. This is not a general utility that would apply to the broad class of polypeptides.

Given the totality of the evidence provided, Applicants submit that they have established a substantial, specific, and credible utility for the claimed polypeptides as diagnostic tools. According to the PTO Utility Examination Guidelines (2001), irrefutable proof of a claimed utility is not required. Rather, a specific, substantial, and credible utility requires only a "reasonable" confirmation of a real world context of use. Applicants remind the PTO that:

> A small degree of utility is sufficient . . . The claimed invention must only be capable of performing some beneficial function . . . An invention does not lack utility merely because the particular embodiment disclosed in the patent lacks perfection or performs crudely . . . A commercially successful product is not required . . . Nor is it essential that the invention accomplish all its intended functions . . . or operate under all conditions . . . partial success being sufficient to demonstrate patentable utility . . . In short, **the defense of non-utility cannot be sustained without proof of total incapacity**. If an invention is only partially successful in achieving a useful result, a rejection of the claimed invention as a whole based on a lack of utility is not appropriate. M.P.E.P. at 2107.01 (underline emphasis in original, bold emphasis added, citations omitted).

Applicants submit that they have established that it is more likely than not that one of skill in the art would reasonably accept the utility for the claimed polypeptides set forth in the specification. In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

Enablement

Claims 1-13 were also rejected under 35 U.S.C. 112, first paragraph. The Examiner asserts that since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art would not know how to use the claimed invention.

As discussed above, Applicants maintain that the claimed polypeptides satisfy the utility requirement. Accordingly, Applicants respectfully request that this rejection be withdrawn.

The Examiner also asserts that even if PRO994 had utility and were enabled, enablement would not be commensurate in scope with Claims 1-5 because the specification does not reasonably provide enablement for polypeptides which are 80, 85, 90, 95 or 99% identical to SEQ ID NO:48.

The Examiner asserts that the specification of provisional application 60/090688 (p. 2, lines 18-20) teaches that PRO994 has (unspecified) homology to the tumor associated-antigen L6 but the instant specification fails to indicate the degree of homology or whether the PRO994 has any homology thereto. The Examiner also asserts that there is no disclosure of any extracellular domain. The Examiner asserts that the claims are broad because they do not require the claimed polypeptides to be identical to the disclosed sequence and because the claims have no functional limitation. The Examiner asserts that the instant specification discloses, however, a single isolated polypeptide sequence SEQ ID NO:48.

The Examiner also maintains that protein function cannot be reliably predicted from sequence homology. The Examiner cites Vukicevic et al. as showing that Transforming Growth Factor (TGF-beta) Family OP-1 induces metanephrongenesis whereas closely related TGF-beta family members-BMP-2 and TGF-beta1 have no effect on metanephrogenesis under identical conditions (Vukicevic et al., 1996, PNAS USA 93:9021-9026), Platelet-derived Growth Factor (PDGF) Tischer et al. is cited as showing that family VEGF, a member of the PDGF family, is mitogenic for vascular endothelial cells but not for vascular smooth muscle cells while PDGF is mitogenic for vascular smooth muscle cells but not for vascular endothelial cells (Tischer et al., U.S. Patent 5,194,596, column 2, line 46 to column 3, line 2). Kopchick et al. is cited as showing that vertebrate growth hormone of 198 amino acids becomes an antagonist (inhibitor of

growth) when a single amino acid is changed (Kopchick et al., U.S. Patent No. 5,350,836). Even 99% homology does not allow predictability in this instance.

Applicants note that as amended herein the claims specify that the claimed polypeptides are more highly expressed in normal stomach or rectum tumor compared to stomach tumor or normal rectum tissue respectively. Furthermore, by virtue of their differential expression, the claimed polypeptides are useful as diagnostic agents or therapeutic agents independent of the homology of the encoded polypeptide to the tumor-associated antigen L6. Applicants note that the claimed invention pertains to the field of recombinant DNA/protein technology and that the level of skill in this field is very high. Furthermore, the measurement of PRO994 expression levels involves routine methodology such as Western Blotting. Levels of PRO994 mRNA can be measured using routine methodology such as Northern Blotting or PCR. In fact, Example 18 describes the measurement of PRO994 mRNA expression levels in biological samples using PCR amplification. The implementation of routine techniques does not constitute undue experimentation. (See *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988).

With respect to the Examiner's concern that small modifications in the sequence encoding a protein may have significant functional consequences, Applicants maintain that the claimed polypeptides can be used for diagnostic or therapeutic purposes even if the activity of the encoded protein has been affected by amino acid differences relative to SEQ ID NO: 47. In particular, Applicants maintain that polypeptides having the recited homology levels to the reference sequences can be used to produce antibodies useful as diagnostic or therapeutic agents. Thus, Applicants maintain the specification enables one skilled in the art to make and use the claimed polypeptides.

The Examiner also asserts that the claims encompass an unreasonable number of inoperative polypeptides, which the skilled artisan would not know how to use. The Examiner maintains that there are no working examples of polypeptides less than 100% identical to SEQ ID NO:48 and that there is only one function potentially attributed to PRO994 (changes in expression in stomach and rectum tumors). According to the Examiner, the specification does not provide guidance for using polypeptides related to (i.e., 80%-99% identity) but not identical to SEQ ID NO:48.

As amended, the pending claims are related to isolated polypeptides having at least 95% or 99% amino acid sequence identity to SEQ ID NO: 48 or portions thereof, and satisfy the limitation "wherein said isolated polypeptide is more highly expressed in normal stomach tissue or rectum tumor compared to stomach tumor or normal rectum tissue respectively, or wherein said isolated polypeptide is encoded by a polynucleotide that is more highly expressed in normal stomach tissue or rectum tumor compared to stomach tumor or normal rectum tissue respectively" or "wherein said isolated polypeptide or a fragment thereof can be used to generate an antibody which can be used to specifically detect the polypeptide of SEQ ID NO: 48 in stomach or rectum tissue samples."

Applicants maintain that there is not substantial variation within the species which fall within the scope of the amended claims, which require at least 95% or 99% amino acid sequence identity to the disclosed sequences related to SEQ ID NO: 48. Applicants note that the pending Claims are analogous to the claims discussed in Example 14 of the written description training materials. In Example 14, the written description requirement was found to be satisfied for claims relating to polypeptides having 95% homology to a particular sequence and possessing a particular catalytic activity, even though the applicant had not made any variants. Similarly, the pending claims also have very high sequence homology to the disclosed sequences and must share the same expression pattern in certain tumors, or share an epitope sufficient to generate antibodies which specifically detect the polypeptide of SEQ ID NO: 48 in stomach or rectum tissue samples.

In Example 14, the procedures for making variants were known in the art and the disclosure taught how to test for the claimed catalytic activity. Similarly, in the instant application, it is well known in the art how to make polypeptides with at least 95% amino acid sequence identity to the disclosed sequences. In addition, the specification discloses how to test to determine if the polypeptide or encoding nucleic acid is differentially expressed in stomach tissue or rectum tissue, and how to make antibodies which specifically detect the polypeptide of SEQ ID NO: 48 in stomach tissue or rectum tissue samples. Like Example 14, the genus of polypeptides that have at least 95% or 99% amino acid sequence identity to the disclosed sequences will not have substantial variation. Although Applicants realize that Example 14 relates to written description rather than enablement, Applicants maintain that because of the lack

of substantial variation within the species encompassed by the claims one skilled in the art would readily be able to make and use the claimed polypeptides.

Furthermore, while Applicants appreciate that actions taken by the PTO in other applications are not binding with respect to the examination of the present application, Applicants note that the PTO has issued many patents containing claims to variant nucleic acids or variant proteins where the applicants did not actually make such nucleic acids or proteins. Representative patents include U.S. Patent No: 6,737,522, U.S. Patent No. 6,395,306, U.S. Patent No. 6,025,156, U.S. Patent No. 6,645,499, U.S. Patent No. 6,498,235, and U.S. Patent No. 6,730,502 which are attached hereto as Exhibits 12-17.

The Examiner also asserts that absent a clear disclosure of which elements of PRO994 are required for its activity, the claims to fusion proteins and variants that are related only by percentage of sequence identity are not fully enabled. According to the Examiner, given the unpredictability of homology comparisons, and the fact that the specification fails to provide objective evidence that the additional sequences are indeed species of the claimed genus it cannot be established that a representative number of species have been disclosed to support the genus claim.

The Examiner asserts that the examples provided in the specification do not provide a representative number of amino acid sequences that would enable a representative number of the polypeptide sequences with assurances that they possess or encode proteins having the desired activity. According to the Examiner, it would require undue experimentation to enable a commensurate number of the sequences that are encompassed by the claims.

As discussed above, Applicants maintain that there is not substantial variation within the species encompassed by the claims. In addition, as discussed above, polypeptides containing the recited levels of homology to reference sequences are useful for generating antibodies useful for diagnostic or therapeutic purposes.

Claims 1-13 were rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. The deposit of biological organisms is considered by the Examiner to be necessary for enablement of the current invention (see 37 C.F.R § 1.808(a)). Examiner acknowledges the deposit of organisms under accession number ATCC 203018 under

terms of the Budapest Treaty on International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure in partial compliance with this requirement. However, the Examiner asserts that in order to be fully compliant with the requirement, applicants must state that the deposit will be maintained for a term of at least 30 years and at least five (5) years after the most recent request for the furnishing of a sample of the deposit was received by the depository.

While Applicants do not concur with the Examiner that the deposit is necessary to enable the claimed invention, Applicants provide a statement herewith containing the language requested by the Examiner.

Written Description

Claims 1-5, 12 and 13 were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The Examiner asserts that the claims do not require that the claimed polypeptides possess any particular biological activity, nor any particular conserved structure, or other disclosed distinguishing feature. The Examiner asserts that the specification of provisional application 60/090688 (p. 2, lines 18-20) teaches that the nucleic acid encoding PRO994 has (unspecified) homology to the nucleic acid which encodes the tumor associated-antigen L6, however the instant specification fails to indicate the degree of homology or whether the PRO994 polypeptide has any homology thereto. The structure of the putative PRO994 peptide is disclosed as comprising four putative transmembrane domains at page 48 of the specification; however, the Examiner asserts that only one of the four, if any, is likely to actually be a transmembrane domain and that it is unclear which end of the protein would be the extracellular domain.

The Examiner asserts that the specification does not provide adequate written description of the claimed genus. According to the Examiner, the protein of SEQ ID NO:48 or active or antigenic fragments thereof, but not the full breadth of the claims meet the written description provision of 35 U.S.C. § 112, first paragraph.

The Legal Standard for Written Description

The well-established test for sufficiency of support under the written description requirement of 35 U.S.C. §112 , first paragraph is whether the disclosure "reasonably conveys to artisan that the inventor had possession at that time of the later claimed subject matter." *In re*

Kaslow, 707 F.2d 1366, 1375, 2121 USPQ 1089, 1096 (Fed. Cir. 1983); *see also Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). The adequacy of written description support is a factual issue and is to be determined on a case-by-case basis. *See e.g., Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). The factual determination in a written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure. *Union Oil v. Atlantic Richfield Co.*, 208 F.3d 989, 996 (Fed. Cir. 2000).

The Current Invention is Adequately Described

As noted above, whether the Applicants were in possession of the invention as of the effective filing date of an application is a factual determination, reached by the consideration of a number of factors, including the level of knowledge and skill in the art, and the teaching provided by the specification. The inventor is not required to describe every single detail of his/her invention. An Applicant's disclosure obligation varies according to the art to which the invention pertains. The present invention pertains to the field of recombinant DNA/protein technology. It is well-established that the level of skill in this field is very high since a representative person of skill is generally a Ph.D. scientist with several years of experience. Accordingly, the teaching imparted in the specification must be evaluated through the eyes of a highly skilled artisan as of the date the invention was made.

As amended, the pending claims are related to isolated polypeptides having at least 95% or 99% amino acid sequence identity to several polypeptides related to SEQ ID NO: 48, and satisfy the limitation "wherein said isolated polypeptide is more highly expressed in normal stomach tissue or rectum tumor compared to stomach tumor or normal rectum tissue respectively, or wherein said isolated polypeptide is encoded by a polynucleotide that is more highly expressed in normal stomach tissue or rectum tumor compared to stomach tumor or normal rectum tissue respectively" or "wherein said isolated polypeptide or a fragment thereof can be used to generate an antibody which can be used to specifically detect the polypeptide of SEQ ID NO: 48 in stomach or rectum tissue samples."

Applicants maintain that there is not substantial variation within the species which fall within the scope of the amended claims, which require at least 95% or 99% amino acid sequence identity to the disclosed sequences related to SEQ ID NO: 48. Applicants note that the pending

Claims are analogous to the claims discussed in Example 14 of the written description training materials. In Example 14, the written description requirement was found to be satisfied for claims relating to polypeptides having 95% homology to a particular sequence and possessing a particular catalytic activity, even though the applicant had not made any variants. Similarly, the pending claims also have very high sequence homology to the disclosed sequences and must share the same expression pattern in certain tumors, or share an epitope sufficient to generate antibodies which specifically detect the polypeptide of SEQ ID NO: 48 in stomach or rectum tissue samples.

In Example 14, the procedures for making variants were known in the art and the disclosure taught how to test for the claimed catalytic activity. Similarly, in the instant application, it is well known in the art how to make polypeptides with at least 95% amino acid sequence identity to the disclosed sequences. In addition, the specification discloses how to test to determine if the polypeptide or encoding nucleic acid is differentially expressed in stomach, or rectum tumors, and how to make antibodies which specifically detect the polypeptide of SEQ ID NO: 48 in stomach or rectum tissue samples. Like Example 14, the genus of polypeptides that have at least 95% or 99% amino acid sequence identity to the disclosed sequences will not have substantial variation.

With respect to the Examiner's assertion that only one of the four transmembrane domains, if any, is likely to actually be a transmembrane domain and that it is unclear which end of the protein would be the extracellular domain, Applicants note that the Examiner has not supplied any basis for his assertion that there is only one transmembrane domain. The features described in Figure 48 for SEQ ID NO: 48 indicate that there are transmembrane domains at amino acids 10-31, 50-72, 87-110 and 191-213. Accordingly, the extracellular domains lie at amino acids 32-49 and amino acids 111-190. Applicants have amended the claims to provide the locations of the extracellular domains.

In conclusion, Applicants submit that they have satisfied the written description requirement for the pending claims based on the actual reduction to practice of SEQ ID NO: 48, by specifying a high level of amino acid sequence identity, by describing how to test for differential expression of the polypeptide and encoding nucleic acid, and by describing how to make antibodies to the disclosed sequence, all of which result in a lack of substantial variability

in the species falling within the scope of the instant claims. Applicants submit that this disclosure would allow one of skill in the art to "recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus." Hence, Applicants respectfully request that the PTO reconsider and withdraw the written description rejection under 35 U.S.C. §112.

Indefiniteness

Claims 1 - 13 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite. According to the Examiner, claims that recite "the extracellular domain" of the protein are indefinite as no extracellular domain has been described. As discussed above, the Examiner asserts that four putative transmembrane domains are disclosed in Figure 48 of the specification but that there is no conception of whether PRO994 is in fact a transmembrane protein, and accordingly, which end of the protein would be the 'extracellular' domain. According to the Examiner, since the protein is predicted to have four transmembrane domains (see Figure 48), it would be predicted to have more than one extracellular domain. Therefore the Examiner maintains that the term "the extracellular domain" is indefinite because it is not clear to which extracellular domain applicant intends to refer. The Examiner asserts that if the protein has a single extracellular domain, the recitation of "the extracellular domain. . .lacking its associated signal sequence" (claim 1, part (d), for example) is indefinite as a signal sequence is not generally considered to be part of an extracellular domain, as signal sequences are cleaved from said domains in the process of secretion from the cell.

As discussed above, Applicants have amended the claims to recite that the extracellular domains are selected from the group consisting of amino acids 32-49 and amino acids 111-190 of SEQ ID NO: 48.

Limitations relating to the "extracellular domain..lacking its associated signal sequences" were also asserted to be indefinite. In the interest of advancing prosecution of this application, Applicants will acquiesce to the PTO's assertion that a signal peptide is not normally considered part of the extracellular domain. By making this concession, Applicants understand that element (c) of Claims 4-6 and 14, as well as Claim 9, describes a polypeptide comprising the extracellular domain of the polypeptide of SEQ ID NO: 48, **lacking** its associated signal peptide. At the same time, as amended, element (d) of Claims 4-6 and 14, as well as Claim 10, describes a polypeptide

comprising the extracellular domain of the polypeptide of SEQ ID NO: 48, **including** its associated signal peptide. Applicants state that this argument is made only in connection with the instant application, and does not reflect the Applicants' interpretation of any claims in any related applications.

For the foregoing reasons, Applicants maintain that the amended claims meet the requirements of 35 U.S.C. §112, second paragraph.

CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

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